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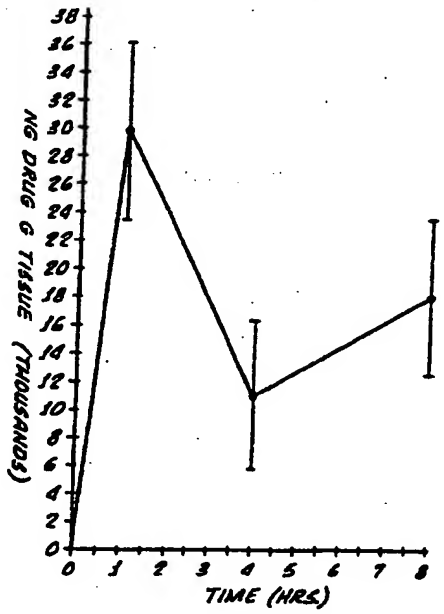

(57) Abstract

A bioerodible drug delivery vehicle with improved flexibility and texture and methods for its use for the controlled administration of a predetermined dosage of at least one pharmaceutical agent for a prolonged period are disclosed and claimed. The vehicle is a generally solid polymeric matrix formed from derivatised cellulose and methacrylic acid copolymer, preferably including a plasticizer and incorporating at least one pharmaceutical agent when placed in a physiological environment such as the cul-de-sac of the eye, the drug delivery vehicle concurrently bioerodes and dispenses the incorporated pharmaceutical agent.

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SUSTAINED RELEASE OF OPHTHALMIC DRUGS FROM A SOLUBLE POLYMER DRUG DELIVERY VEHICLE

Field of the Invention

The present invention relates in general to drug delivery vehicles and methods for the continuous and prolonged administration of pharmaceutical compounds to a patient. More particularly, this invention relates to ocular drug dispensing devices which contain at least one pharmaceutical agent. Placed in the physiological environment of the eye, the drug delivery vehicles of the present invention concurrently bioerode and dispense therapeutically desired amounts of the pharmaceutical agents. In another aspect, the invention relates to methods of using these devices to deliver therapeutic amounts of such compounds to the eye.

Background of the Invention

The effectiveness of a drug depends not only on the active substances it contains, but also -- and to a quite important extent -- on the nature of its preparation, i.e., formulation and processing necessary to produce the appropriate dosage form.

A widely applicable formulation for drug delivery systems involves polymeric devices that can controllably deliver a drug for a prolonged period by erosion into toxicologically harmless degradation products. Prolonged or sustained release technology exploits the relationship between release rate of the active pharmaceutical agent and quantity of polymers. In part, such consideration allows a certain predictability in release rates to be made.

In the 1950's semi-synthetic, cellulose derivative drug delivery vehicles, such as methyl cellulose and cellulose acetate phthalates were introduced, as well as the wholly synthetic polymethacrylic esters. These vehicles had specific solubility characteristics adapted to the pH conditions in the human digestive tract.

Probably the most important application of polymethacrylates in the pharmaceutical industry is as special adjuvants in galenic formulation, primarily to coat oral dosage forms and to regulate drug release rates. They are used in transdermal preparation for cutaneous use and film coatings for oral use. Their important qualities are a high stability to environmental factors during storage and high biocompatibility, i.e., neutrality with respect to tissue and body fluids, and their solubility properties have been adapted to suit the conditions in the digestive tract.

In this context the term "bioerodible" is defined as the property or characteristic of a body or a microporous, solid or gel material to innocuously disintegrate or break down as a unit structure or entity, over a prolonged period of time, in response to the physiological environment by one or more physical or chemical degradative processes. For example, a bioerodible drug delivery vehicle for the eye could disintegrate as a result of enzymatic action, oxidation or reduction, hydrolysis (proteolysis), displacement, e.g., ion exchange, or dissolution by solubilization, emulsion or micelle formation. In the exemplary ocular environment, the polymeric materials of the vehicle are absorbed by the eye and surrounding tissues and are otherwise dissipated, such as by elimination from the ocular cavity to the punctum with tear fluid.

Exemplary prior art ocular inserts which provide controlled drug dispensing and which do not have to be removed from the eye have been disclosed in U.S. Patent

No.s 3,960,150, 3,981,303 and 3,993,071. Generally, these inserts provide a body of bioerodible drug-release-rate controlling material containing a drug. Typically, the body of the insert is of an initial shape which is adapted for insertion and retention in the cul-de-sac of the eye bounded by the surfaces of the bulbar conjunctiva of the eye sclera of the eyeball and the palpebral conjunctiva of the lid. The body of the ocular insert provides a flow of a therapeutically effective amount of drug to the eye at a controlled rate over a prolonged period of time as the body bioerodes in the environment of the eye concurrently with the dispensing or at a point in time after the dispensing of the therapeutically desired amount of drug.

Prior art materials known to be generally suitable for use as the bioerodible drug release rate controlling material (either as membrane or matrix materials) of ocular inserts are: (1) hydrolytically biodegradable polyanhydride polymers, (2) polyesters which are typically polymerization condensation products of monobasic hydroxy acids, such as lactic and/or glycolic acid, (3) cross-linked, anionic polyelectrolytes, comprising substantially water insoluble polymeric coordination complexes, (4) cross-linked gelatin materials, and (5) other materials which slowly bioerode into liquids, such as (a) structural proteins in hydrocolloids of animal origin, (b) polysaccharides and other hydrocolloids of plant origin, and (c) synthetic polymers.

Ophthalmic inserts are beneficial for several therapeutic indications. First of all, delivery of drugs such as antibiotics that have to be administered as many as eight times a day would be significantly easier with erodible inserts. The inserts could be administered once daily or perhaps even once weekly. The drug would slowly dissolve out of the matrix and into the tear film, where it would be absorbed by the tissue at the site of action. Since the matrix is soluble, the insert would not have to

be removed from the eye once the drug contained in the insert is completely released. Drugs that have a short half-life in the body, such as peptides, growth factors, or glaucoma drugs could also be administered from the inserts. A further use for such inserts is with the delivery of drugs that sting or cause ocular discomfort. It would be advantageous to have a device that would allow sustained delivery of these drugs below a "stinging threshold." Delivery of such drugs from an insert is likely to increase bioavailability of the drug, making it easier for patients to comply with this particular dosage form as compared to a traditional dropper bottle format.

A major disadvantage of known ocular inserts is the discomfort and pain that may occur when they are installed. Also, patients may have difficulty placing inserts into the cul-de-sac of the eye if their dexterity is impaired, as is often the case with elderly people. A further disadvantage of bioerodible ocular inserts is the discomfort and vision blurring caused by very rapid swelling of the insert, with concomitant rapid dumping of the drug in the precorneal fluid. Such disadvantages are typical with cellulose polymer inserts.

Therefore, it would be highly desirable to have a drug delivery insert comprised of a material that can be formed into a shape suitable for retention in a particular anatomic location that has a softness which does not cause discomfort upon installation that does not uncontrollably lose its shape by rapidly swelling, and which has desirable rate-releasing properties to provide controlled, prolonged therapeutic release of one or more drugs from the insert.

Further, there is a need for a drug delivery device that dissolves under physiological conditions into harmless by-products, that contains an ophthalmic pharmaceutical compound dispersed within it, that bioerodes to dispense the compound at a therapeutically

desirable rate, that can be comfortably inserted within the eye, that remains comfortable to the patient when it is in the eye, and which improves the ocular bioavailability of the pharmaceutical compound while dispensing.

Summary

In accordance with the teachings of the present invention, bioerodible drug delivery vehicles for the controlled continuous administration of predetermined dosages of at least one pharmaceutical agent are provided which overcome the above mentioned problems and provide controlled delivery characteristics for prolonged periods of time with improved flexibility and texture.

The present invention is directed to bioerodible drug delivery vehicles for the controlled continuous administration of predetermined dosages of at least one pharmaceutical agent for prolonged periods of time. In accordance with the teaching of the present invention the vehicles provide improved delivery characteristics, flexibility and texture. In a broad aspect the drug delivery vehicles of the present invention comprise a generally solid polymeric matrix formed of a mixture of derivatised cellulose polymer and methacrylic acid copolymer. Where desired, plasticizer may be included. Additionally, at least one pharmaceutical agent is dispersed within the polymeric matrix of the bioerodible drug delivery vehicle. When placed in a physiological environment, the polymeric matrix bioerodes concurrently with the dispensing of a therapeutically desired amount of at least one pharmaceutical agent.

In an alternative embodiment of the present invention the drug delivery vehicle is provided with an initial shape adapted for insertion and retention in the cul-de-sac of the eye.

Another aspect of the invention resides in a method of administering a predetermined dosage of at least one pharmaceutical compound or agent to the eye. The method comprises the steps of inserting into the eye the bioerodible drug delivery vehicle of the present invention, which thereby dispenses the pharmaceutical agent in a therapeutically effective amount to the eye in a substantially continuous manner.

The above discussed and many other features and attendant advantages of the present invention, as well as a better understanding thereof, will be afforded to those skilled in the art from a consideration of the following detailed explanation of preferred exemplary embodiments thereof. Reference will be made to the appended sheets of drawings which will now be first described briefly.

Brief Description of the Drawings

Fig. 1 is a graphical representation of a drug release profile obtained with an exemplary embodiment of the present invention and illustrating the features thereof.

Fig. 2 is a graphical representation of an alternative drug release profile of an exemplary embodiment of the present invention.

Fig. 3 is a graphical representation of various drug release profiles illustrating the stability of the drug delivery vehicles of the present invention.

Detailed Description of the Invention

In general, the present invention provides bioerodible drug delivery vehicles for the controlled, continuous administration of predetermined dosages of at least one pharmaceutical agent for prolonged periods of time. The drug delivery vehicles have improved drug delivery characteristics, as well as improved physical flexibility and texture. The present invention also

provides methods of using the bioerodible drug delivery vehicles of the present invention. In a broad aspect, the methods involve inserting into the eye or other similar physiological environments the drug delivery vehicles of the present invention. In these methods, predetermined dosages of at least one pharmaceutical agent can be delivered to the eye in a therapeutically effective amount in a substantially continuous manner. When positioned in the eye the bioerodible drug delivery vehicle of the present invention achieves a dosage form that increases the drug residence time in the precorneal area, which in turn improves the ocular bioavailability of the drug while keeping the drug concentration low.

More specifically, in a preferred exemplary embodiment of the present invention the bioerodible drug delivery vehicle comprises a generally solid polymeric matrix, an optional plasticizer, and at least one pharmaceutical agent dispersed within the polymeric matrix. The generally solid polymeric matrix is formed from a mixture of derivatised cellulose polymer and methacrylic acid copolymer. The derivatised cellulose polymer preferably is selected from the group including, but not restricted to, hydroxypropyl-methylcellulose (HPMC), hydroxypropyl-ethylcellulose, and hydroxy-ethyl cellulose (HEC). In the exemplary embodiments of the present invention the preferred derivatised cellulose polymer is HPMC. Hydroxypropyl-methylcellulose is available from Dow Chemical under the trade name Methocel having mole weights ranging from 50 to 500 KiloDaltons. The methacrylic acid copolymer comprising the solid polymeric matrix preferably is selected from the group including, but not restricted to, methyl-methacrylate and methacrylic acid copolymer, and ethyl-methacrylate methacrylic acid copolymer. In the preferred exemplary embodiments the preferred methacrylic acid copolymer is methyl-methacrylate and methacrylic acid copolymer. This

methacrylic acid copolymer is available from Röhm Pharma under the trade name Eudragit and may be purchased in mole ratios ranging from 1:1 to 1:2 and molecular weights ranging from 50 to 500 KiloDaltons.

The generally solid polymeric matrix preferably is formed by mixing derivatised cellulose polymer and methacrylic acid copolymer using conventional mixing techniques. For example, as described below in Example I, the crystalline forms of derivatised cellulose polymer and methacrylic acid copolymer are simply blended and the blend is mixed with plasticizer containing a pharmaceutical compound to form a powder. The powder so formed is then placed in a melt extruder, which extrudes rods of the generally solid polymeric matrix incorporating the pharmaceutical compound. In a preferred embodiment, the bioerodible drug delivery vehicle is formed by mixing derivatised cellulose polymer to methacrylic acid copolymer in a ratio from about 1:10 to about 10:1 by weight. In particular, an exemplary embodiment of the drug delivery vehicle of the present invention employs a ratio of HPMC to methacrylic acid copolymer of from about 1:3 to about 3:1. A typical operable ratio in the present invention of HPMC to methacrylic acid copolymer is about 1.6 : 1 by weight.

The bioerodible drug delivery vehicle of the present invention may be readily adapted for insertion and retention in the cul-de-sac of the eye. Thus, a particularly useful embodiment of the present invention is directed to a bioerodible ocular drug delivery vehicle. The invention achieves this adaptation by providing the drug delivery vehicle with an initial shape adapted for insertion and retention in the cul-de-sac of the eye. An operable shape for such use has been found to be a generally cylindrical rod or barrel having a diameter of about 0.25 mm to about 3 mm and a length of from about 1 mm to about 20 mm.

This embodiment of the bioerodible drug delivery vehicle provides an advantageous shape and texture in that it does not lose its shape by swelling so rapidly in the cul-de-sac of the eye as to cause discomfort and blurring of vision.

The prolonged, controlled dissolution of the bioerodible drug delivery vehicle is based on the unique and unanticipated compatibility of the cellulose derivative with the methacrylic acid copolymer. It was not anticipated that this blend of polymers, either alone or in combination with a plasticizer would form a compatible, homogenous, transparent insert which would not undergo phase separation. Additionally, the texture of the bioerodible drug delivery vehicle, the retention time, and the release rate of the drug from the vehicle can be controlled by varying the ratio of the more hydrophobic component, the methacrylic acid copolymer, to the more hydrophilic component, the derivatised cellulose polymer. Higher derivatised cellulose polymer concentrations produce bioerodible drug delivery vehicles with softer, more comfortable textures. Additionally, by providing sufficient concentrations of the hydrophobic methacrylic acid copolymer the softness of the insert can be maintained while preventing the rapid, uncontrolled swelling of the insert with concomitant rapid dumping of the drug into the target physiologic site. Further, unique blends of these polymers can be tailored to provide drug delivery vehicles that sustain comfortable delivery of the drug to a target site over periods of 24 hours or more.

Moreover, unlike prior art erodible drug delivery vehicles which erode from the outer surface to the core, the drug delivery vehicles of the present invention undergo controlled dissolution in a different manner. More specifically, drug delivery vehicles formed from the exemplary blends of cellulose derivatives and methacrylic

acid copolymers undergo a controlled simultaneous dissolution of both the outer layers and inner core of the polymeric matrix. Thus, varying surface area to volume ratios have a lesser impact on the dissolution and drug delivery rates relative to the prior art.

As noted above, it is contemplated as being within the scope of the present invention to incorporate at least one pharmaceutical agent dispersed within the generally solid polymeric matrix of the drug delivery vehicle. Exemplary pharmaceutical agents include oligopeptides, antibacterials, antihistaminics, anti-inflammatories, miotics, anticholinergics, mydriatics, antiglaucomals, antiparasitics, antivirals, carbonic anhydrase inhibitors, antifungals, anesthetics, diagnostic and immunosuppressive agents. More specifically, it is contemplated as being within the scope of the present invention to incorporate therapeutic or diagnostic compounds such as epidermal growth factor, dipivalyl epinephrine hydrochloride, levo-bunolol hydrochloride, UK-14304-18, pilocarpine, sodium fluorescein, tetracycline, chlortetracycline, bacitracin, neomycin, polymyxin, gramicidin, tobramycin, ciprofloxacin, norfloxacin, penicillin, erythromycin, cefazolin, ceftazadime, imipenem, idoxuridine, hydrocortisones, dexamethasone, dexamethasone 21 phosphate, fluocinolone, medrysone, prednisolone acetate, fluormetholone, betamethasone, phenylephrine, eserine salicylate, carbachol, echothiophate iodide, demecarium bromide, cyclopentolate, homatropine, scopolamine, epinephrine, ibuprofen, aceclidine, tretinoin, and pirenoxine.

Drug delivery vehicles produced in accordance with the teachings of the present invention can be configured to bioerode in a physiological environment over prolong periods of time ranging from approximately 2 hours to 48 hours. Modification of the erosion rate can be achieved through several different manners. For example, the

polymer ratios can be varied from 1:10 to 10:1. Alternatively, the size and available surface area of the insert may be varied as well. As those skilled in the art will appreciate, varying the dissolution or erosion profile will vary the drug delivery profile as well. Similarly, varying the concentration of pharmaceutical agent incorporated in the polymeric matrix will also affect the drug release rate. Along these lines, it is contemplated as being within the scope of the present invention to incorporate the pharmaceutical agent or agents of interest in quantities ranging from 0.01% to 30% by weight.

The drug delivery vehicle of the present invention may also be utilized in a novel method of administrating pharmaceutical agents to aqueous physiological environments such as the eye. As noted above, a suitably shaped pharmaceutical drug delivery vehicle insert can be positioned within the cul-de-sac of the eye where it is stably retained. Enhancing this functional utility, the drug delivery vehicles of the present invention exhibit previously unattainable softness and comfort upon installation in the eye and do not uncontrollably lose their shape by rapid swelling. Rather, the drug delivery vehicles of the present invention exhibit a comfortable controlled dissolution over a prolonged period of time in conjunction with a controlled therapeutic release of the incorporated pharmaceutical agent or agents. Moreover, the bioerodible inserts of the present invention do not require removal by trained medical personnel at the end of the desired drug delivery cycle. Rather, they harmlessly dissolve and are expelled from the physiological target site or from the eye into the lacrimal drainage system.

A further understanding of the sustained release drug delivery vehicles of the present invention will be afforded to those skilled in the art from the following non-limiting examples of exemplary embodiments thereof.

Example I

FORMULATION OF DRUG DELIVERY VEHICLES

An exemplary drug delivery vehicle illustrating the features of the present invention was formulated from Eudragit S100, Methocel J4, propylene glycol and sodium flurbiprofen in the proportions, by weight, of 48:30:20:2. It was manufactured as follows: Crystalline sodium flurbiprofen was dissolved in propylene glycol, to form a plasticizer solution. The propylene glycol was obtained from Aldrich Chemicals, St. Louis, MO. In a separate vessel, crystalline Eudragit S100 and Methocel J4 were blended. Eudragit S100 was obtained from Rohm Pharma, Weiterstadt, Germany. Methocel J4 was obtained from Dow Chemicals, Midland, MI. The plasticizer solution was then added to the blend of Eudragit S100 and Methocel J4, and blended thoroughly, yielding a powder. The powder was then added to a melt extruder obtained from Custom Scientific Instruments, Cedar Knolls, NJ and allowed to mix for about one minute. The melt extruder was maintained at 160° C. Rods were then extruded from the melt extruder and cut into desired lengths. The diameter of the rods was determined by the diameter of the mold placed in the extruder, and was varied from 0.5 mm up to 2 mm. These rods were used as bioerodible drug delivery vehicles or inserts in the Examples below.

EXAMPLE II

PROLONGED CONTINUOUS RELEASE OF DRUG

Twelve New Zealand albino rabbits (24 eyes) were dosed with the bioerodible drug delivery vehicles or inserts of the present invention. All nictitating membranes had been removed two weeks prior to the experiment. The 1 mm diameter inserts weighed from 5 to 8 mg each and varied in length from 5 mm to 7 mm. The inserts containing Eudragit S100, Methocel J4 propylene glycol and sodium flurbiprofen in percent by weight

proportions of 48:30:20:2 were prepared as in Example I, above.

At various time points after placement of the inserts in the cul-de-sac of the eye, each insert was removed, weighed, and analyzed for the amount of drug remaining in it. The weights of the inserts and amount of drug remaining in the inserts are shown in Table 1, below. Additionally, the aqueous humor, lower and upper conjunctiva tissues of the rabbit were analyzed for flurbiprofen content to establish concentration time profiles, as shown in Figures 1 and 2.

TABLE 1

Weights of Inserts and Amount of Drug Remaining in Insert.

Hours	# Inserts Present	Avg. % weight remaining	Avg. % FBP remaining
0	100%	84.2 ± 1.5%	83.4%
1	100%	71.6 ± 3.6%	67.9%
8	100%	64.1 ± 10.7%	0.80%
24	33.3%	2.0 ± 5.0%	0.01%
30	16.7%	7.9 ± 19.4%	0.01%

As graphically illustrated in Figs. 1 and 2, these results indicate that there was sustained release of flurbiprofen from the inserts over at least 8 hours, and that there was a corresponding prolonged, continuous delivery of the drug to the lower conjunctiva tissue (Figure 1) and the upper conjunctiva tissue (Figure 2). The concentration of flurbiprofen was fifty to one hundred times greater in the lower conjunctiva tissue than in the upper conjunctiva. This was probably due to placement of the insert in the lower cul-de- sac.

EXAMPLE III

GAMMA STERILIZATION OF DRUG DELIVERY VEHICLE

Drug delivery vehicles prepared according to the method of Example I, above, were gamma-irradiated at 0.9-1.1 Mrad and 2.4-2.6 Mrad. Standard, well-known methods were used to irradiate the vehicles. The shelf stability of the irradiated vehicles was then determined by storing them for up to 11 weeks.

The results, as shown below in Table 2, and as illustrated in Fig. 3, indicate that the vehicles were stable after the sterilization process was completed. Gamma irradiation left the polymer and drug intact. After 11 weeks of storage at 23° C, the flurbiprofen content was at least 90% recoverable from the vehicles. Gamma irradiation had minimal effect on the polymer structure and did not lead to polymer breakdown or to rapid, uncontrolled release of the drug from the vehicle.

Table 2

Recovery of Flurbiprofen from Stored Gamma-Sterilized Inserts

TIME Sample	% flurbiprofen in rod	% recovery
2 weeks		
No gamma	2.32	
1.1-1.2 Mrad	2.12	91.4
2.3 Mrad	2.16	93.1
6 weeks		
No gamma, 4°C	1.96	
No gamma, 23°C	1.98	101.0
No gamma, 37°C	2.01	102.6
1.1-1.2 Mrad, 4°C	1.95	99.5
1.1-1.2 Mrad, 23°C	1.89	96.4
1.1-1.2 Mrad, 37°C	1.97	100.5
2.3 Mrad, 4°C	1.91	97.4
2.3 Mrad, 23°C	1.90	96.9
2.3 Mrad, 37°C	1.83	93.4
11 weeks		
No gamma	1.96	
1.1-1.2 Mrad	1.93	98.5
2.3 Mrad	1.89	96.4

EXAMPLE IV

RETENTION OF DRUG DELIVERY VEHICLE IN THE EYE

This study determined how long the drug delivery vehicle took to dissolve in the cul-de-sac of owl monkeys, which have a blink rate similar to humans. The owl monkey (Aotus trivirgatus) blinks about 10-15 times per minute. Placebo inserts containing 49.5% Eudragit S100, 29.7% Methocel J4, and 20.8% propylene glycol were inserted into the cul-de-sac of the monkeys and into the cul-de-sacs of rabbits, which blink about 3 times per hour. As shown below in Table 3, the insert dissolved faster in the monkey than in the rabbit model. It was observed that the monkeys had no apparent problems or discomfort while retaining the drug delivery vehicles placed in the cul-de-sac for at least eight hours.

TABLE 4

Summary of Weight Loss Data In Vivo

	Time	% weight loss
Rabbit	3 hours	7% (n = 4)
	7 hours	20% (n = 2)
Owl monkey	3 hours	23% (n = 2)
	8.1 hours	48% (n = 1)

It is apparent that many modifications and variations of this invention, as set forth above, may be made without departing from the spirit and scope thereof. The specific embodiments described are given by way of example only, and the invention is limited only by the terms of the appended claims.

CLAIMS

What is claimed is:

1. A bioerodible drug delivery vehicle for the controlled administration of a predetermined dosage of at least one pharmaceutical agent for a prolonged period of time and having improved delivery characteristics, flexibility and texture, said drug delivery vehicle comprising:

a generally solid polymeric matrix, formed of a mixture of derivatised cellulose polymer and methacrylic acid copolymer;

a plasticizer; and

at least one pharmaceutical agent dispersed within said polymeric matrix

2. The drug delivery vehicle of Claim 1 wherein said derivatised cellulose polymer is selected from the group consisting of hydroxypropyl-methylcellulose, hydroxypropyl-ethylcellulose, hydroxypropyl methylcellulose phthalate, and methyl cellulose.

3. The drug delivery vehicle of Claim 1 wherein said methacrylic acid copolymer is selected from the group consisting of methyl-methacrylate and methacrylic acid copolymer, and ethyl-methacrylate methacrylic acid copolymer.

4. The drug delivery vehicle of Claim 1 wherein said derivatised cellulose polymer and methacrylic acid copolymer comprise a mixture having a ratio of from about 1:10 to about 10:1 derivatised cellulose polymer to methacrylic acid copolymer by weight.

5. The drug delivery vehicle of Claim 1 wherein said derivatised cellulose polymer is hydroxypropyl-methylcellulose and said methacrylic acid copolymer is methyl-methacrylate methacrylic acid copolymer.

6. The drug delivery vehicle of Claim 5 wherein the ratio of hydroxypropyl-methylcellulose to methyl-methacrylate and methacrylic acid copolymer is about 1 : 1.6 by weight.

7. The drug delivery vehicle of Claim 1 wherein said vehicle is provided with an initial shape which is adapted for insertion and retention in the cul-de-sac of the eye.

8. The drug delivery vehicle of Claim 7 wherein said initial shape is a generally cylindrical rod having a diameter of from about 0.5 mm to about 2.0 mm and a length of from about 4 mm to about 15 mm.

9. The drug delivery vehicle of Claim 1 wherein said at least one pharmaceutical agent is selected from at least one of the group consisting of protein growth factors, oligopeptides, antibacterials, antihistaminics, anti-inflammatories, miotics, anticholinergics, mydriatics, antiglaucomals, antiparasitics, antivirals, carbonic anhydrase inhibitors, antifungals, anesthetics, diagnostic and immunosuppressive agents .

10. A method of administering a predetermined dosage of at least one pharmaceutical agent to the eye, said method comprising the steps of inserting into the eye the bioerodible drug delivery vehicle of Claim 7; and

allowing the inserted vehicle to bioerode to thereby dispense the pharmaceutical agent in a therapeutically effective amount to the eye.

11. A bioerodible ocular drug delivery vehicle for the controlled administration of a predetermined dosage of at least one pharmaceutical agent for a prolonged period of time to the eye and having improved delivery characteristics, flexibility and texture, said drug delivery vehicle comprising:

a generally solid rod shaped polymeric matrix formed of a mixture of derivatised cellulose polymer and methacrylic acid copolymer;

a plasticizer; and

at least one pharmaceutical agent dispersed within said polymeric matrix whereby said polymeric matrix bioerodes in the eye concurrently with the dispensing of the therapeutically desired amount of said at least one pharmaceutical agent.

12. The ocular drug delivery vehicle of Claim 11 wherein said derivatised cellulose polymer is selected from the group consisting of hydroxypropyl-methylcellulose, hydroxypropyl-ethylcellulose, hydroxypropyl methylcellulose phthalate, and methylcellulose.

13. The ocular drug delivery vehicle of Claim 11 wherein said methacrylic acid copolymer is selected from the group consisting of methyl-methacrylate and methacrylic acid copolymer, ethyl-methacrylate and methacrylic acid.

14. The ocular drug delivery vehicle of Claim 11 wherein the ratio of said derivatised cellulose polymer to said methacrylic acid copolymer is from about 1:10 to about 10:1 by weight.

15. The ocular drug delivery vehicle of Claim 11 wherein said derivatised cellulose polymer is

hydroxypropyl-methylcellulose and said methacrylic acid copolymer is methyl-methacrylate methacrylic acid copolymer.

16. The ocular drug delivery vehicle of Claim 15 wherein said ratio of hydroxypropyl-methylcellulose to methyl-methacrylate and methacrylic acid copolymer is about 1 : 1.6 by weight.

17. The ocular drug delivery vehicle of Claim 11 wherein said rod is generally cylindrical having a diameter of from about 0.5 mm to about 2 mm and a length of from about 4 mm to about 15 mm.

18. The ocular drug delivery vehicle of Claim 11 wherein said at least one pharmaceutical agent is selected from at least one of the group consisting of protein growth factors, oligopeptides, antibacterials, antihistaminics, anti-inflammatories, miotics, anticholinergics, mydriatics, antiglaucomals, antiparasitics, antivirals, carbonic anhydrase inhibitors, antifungals, anesthetics, diagnostic and immunosuppressive agents .

AMENDED CLAIMS

[received by the International Bureau on 21 January 1994 (21.01.94); original claims 1,4 and 11 amended; other claims unchanged (4 pages)]

1. A bioerodible drug delivery vehicle for the controlled administration of a predetermined dosage of at least one pharmaceutical agent for a prolonged period of time and having improved delivery characteristics, flexibility and texture, said drug delivery vehicle comprising:

a generally solid polymeric matrix, formed of a substantially homogeneous blend of derivatised cellulose polymer and methacrylic acid copolymer;

a plasticizer; and

at least one pharmaceutical agent uniformly dispersed within said polymeric matrix

2. The drug delivery vehicle of Claim 1 wherein said derivatised cellulose polymer is selected from the group consisting of hydroxypropyl-methylcellulose, hydroxypropyl-ethylcellulose, hydroxypropyl methylcellulose phthalate, and methyl cellulose.

3. The drug delivery vehicle of Claim 1 wherein said methacrylic acid copolymer is selected from the group consisting of methyl-methacrylate and methacrylic acid copolymer, and ethyl-methacrylate methacrylic acid copolymer.

4. The drug delivery vehicle of Claim 1 wherein said derivatised cellulose polymer and methacrylic acid copolymer comprise a substantially homogeneous blend having a ratio of from about 1:10 to about 10:1 derivatised cellulose polymer to methacrylic acid copolymer by weight.

5. The drug delivery vehicle of Claim 1 wherein said derivatised cellulose polymer is hydroxypropyl-methylcellulose and said methacrylic acid copolymer is methyl-methacrylate methacrylic acid copolymer.

6. The drug delivery vehicle of Claim 5 wherein the ratio of hydroxypropyl-methylcellulose to methyl-methacrylate and methacrylic acid copolymer is about 1 : 1.6 by weight.

7. The drug delivery vehicle of Claim 1 wherein said vehicle is provided with an initial shape which is adapted for insertion and retention in the cul-de-sac of the eye.

8. The drug delivery vehicle of Claim 7 wherein said initial shape is a generally cylindrical rod having a diameter of from about 0.5 mm to about 2.0 mm and a length of from about 4 mm to about 15 mm.

9. The drug delivery vehicle of Claim 1 wherein said at least one pharmaceutical agent is selected from at least one of the group consisting of protein growth factors, oligopeptides, antibacterials, antihistaminics, anti-inflammatories, miotics, anticholinergics, mydriatics, antiglaucomals, antiparasitics, antivirals, carbonic anhydrase inhibitors, antifungals, anesthetics, diagnostic and immunosuppressive agents .

10. A method of administering a predetermined dosage of at least one pharmaceutical agent to the eye, said method comprising the steps of inserting into the eye the bioerodible drug delivery vehicle of Claim 7; and

allowing the inserted vehicle to bioerode to thereby dispense the pharmaceutical agent in a therapeutically effective amount to the eye.

11. A bioerodible ocular drug delivery vehicle for the controlled administration of a predetermined dosage of at least one pharmaceutical agent for a prolonged period of time to the eye and having improved delivery characteristics, flexibility and texture, said drug delivery vehicle comprising:

a generally solid rod shaped polymeric matrix formed of a substantially homogeneous blend of derivatised cellulose polymer and methacrylic acid copolymer;

a plasticizer; and

at least one pharmaceutical agent uniformly dispersed within said polymeric matrix whereby said polymeric matrix bioerodes in the eye concurrently with the dispensing of the therapeutically desired amount of said at least one pharmaceutical agent.

12. The ocular drug delivery vehicle of Claim 11 wherein said derivatised cellulose polymer is selected from the group consisting of hydroxypropyl-methylcellulose, hydroxypropyl-ethylcellulose, hydroxypropyl methylcellulose phthalate, and methylcellulose.

13. The ocular drug delivery vehicle of Claim 11 wherein said methacrylic acid copolymer is selected from the group consisting of methyl-methacrylate and methacrylic acid copolymer, ethyl-methacrylate and methacrylic acid.

14. The ocular drug delivery vehicle of Claim 11 wherein the ratio of said derivatised cellulose polymer to said methacrylic acid copolymer is from about 1:10 to about 10:1 by weight.

15. The ocular drug delivery vehicle of Claim 11 wherein said derivatised cellulose polymer is

hydroxypropyl-methylcellulose and said methacrylic acid copolymer is methyl-methacrylate methacrylic acid copolymer.

16. The ocular drug delivery vehicle of Claim 15 wherein said ratio of hydroxypropyl-methylcellulose to methyl-methacrylate and methacrylic acid copolymer is about 1 : 1.6 by weight.

17. The ocular drug delivery vehicle of Claim 11 wherein said rod is generally cylindrical having a diameter of from about 0.5 mm to about 2 mm and a length of from about 4 mm to about 15 mm.

18. The ocular drug delivery vehicle of Claim 11 wherein said at least one pharmaceutical agent is selected from at least one of the group consisting of protein growth factors, oligopeptides, antibacterials, antihistaminics, anti-inflammatories, miotics, anticholinergics, mydriatics, antiglaucomals, antiparasitics, antivirals, carbonic anhydrase inhibitors, antifungals, anesthetics, diagnostic and immunosuppressive agents.

STATEMENT UNDER ARTICLE 19

To further define the present invention and to clarify the features which differentiate it from the references cited by the International Searching Authority, claims 1, 4 and 11 have been amended to emphasize that the subject drug delivery vehicles are formed of a bioerodible polymeric matrix comprising a unique, substantially homogeneous blend of derivatised cellulose and methacrylic acid copolymer previously thought to be immiscible.

In contrast, the first reference cited by the International Searching Authority, Japanese patent application 1 071 822, is directed to a suspension of individual hydrophobic granules, such as non-erodible methacrylate particles, dispersed in a hydrophilic polymeric composition. There is no disclosure or suggestion that the immiscible polymers used to form this suspension could be homogeneously blended, much less that they can be used to fabricate a bioerodible, slow release, comfortable drug delivery vehicle such as that of the present invention. Thus, the continued presence of the non-erodible hydrophobic particles will substantially increase the likelihood of patient discomfort.

European Patent Application 0 077 261, also cited by the International Searching Authority, discloses ocular inserts using low molecular weight polyvinyl alcohol as the principal material to give the insert its desired shape and integrity. Although other polymers, including hydroxypropyl cellulose and enteric coating materials, may be incorporated in the insert, this reference provides no disclosure or suggestion that the immiscible derivatised cellulose and methacrylic acid copolymers can be blended to provide a homogeneous matrix which comfortably erodes in the eye as disclosed in the present application.

Accordingly, the claimed invention as reflected in these amended claims is both novel and inventive with respect to these references.

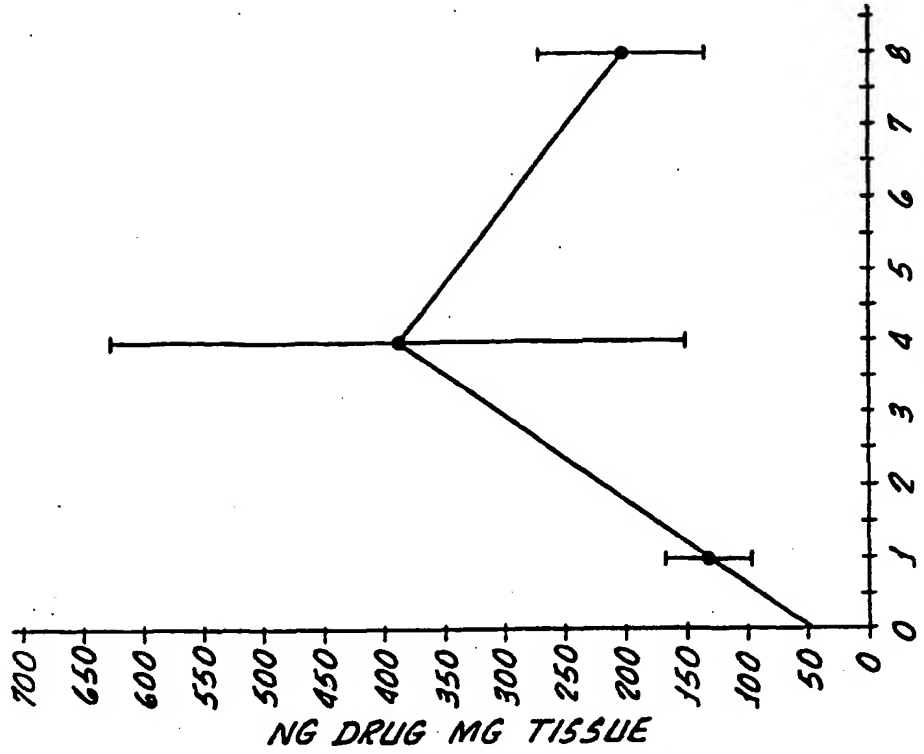
NG DRUG MG TISSUE
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
0 1 2 3 4 5 6 7 8
TIME (HRS.)

FIG. 2.

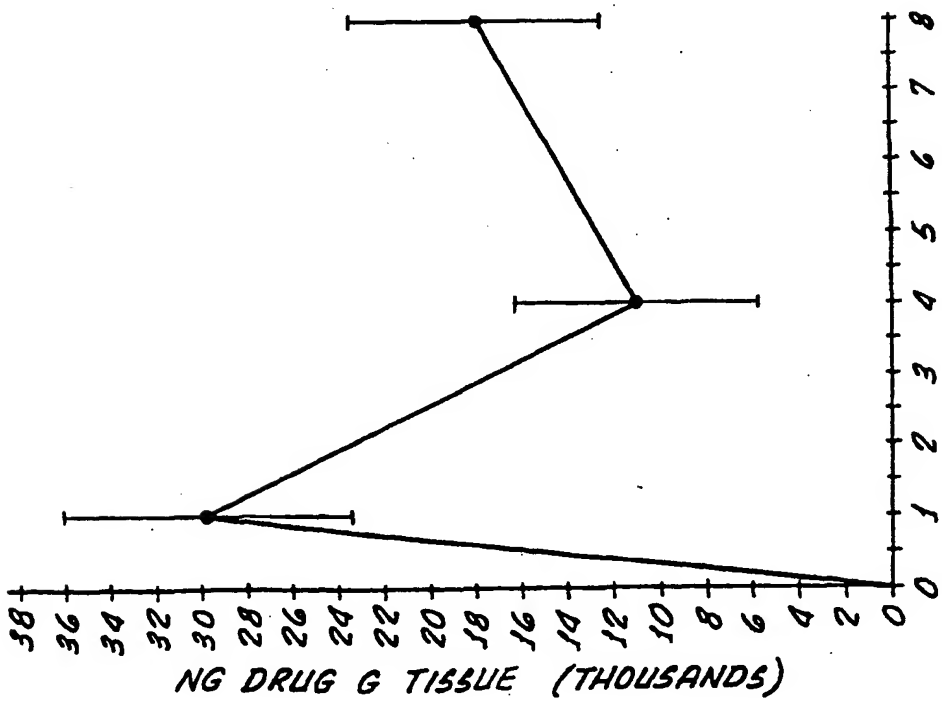
NG DRUG G TISSUE (THOUSANDS)
38
36
34
32
30
28
26
24
22
20
18
16
14
12
10
8
6
4
2
0
0 1 2 3 4 5 6 7 8
TIME (HRS.)

FIG. 1.

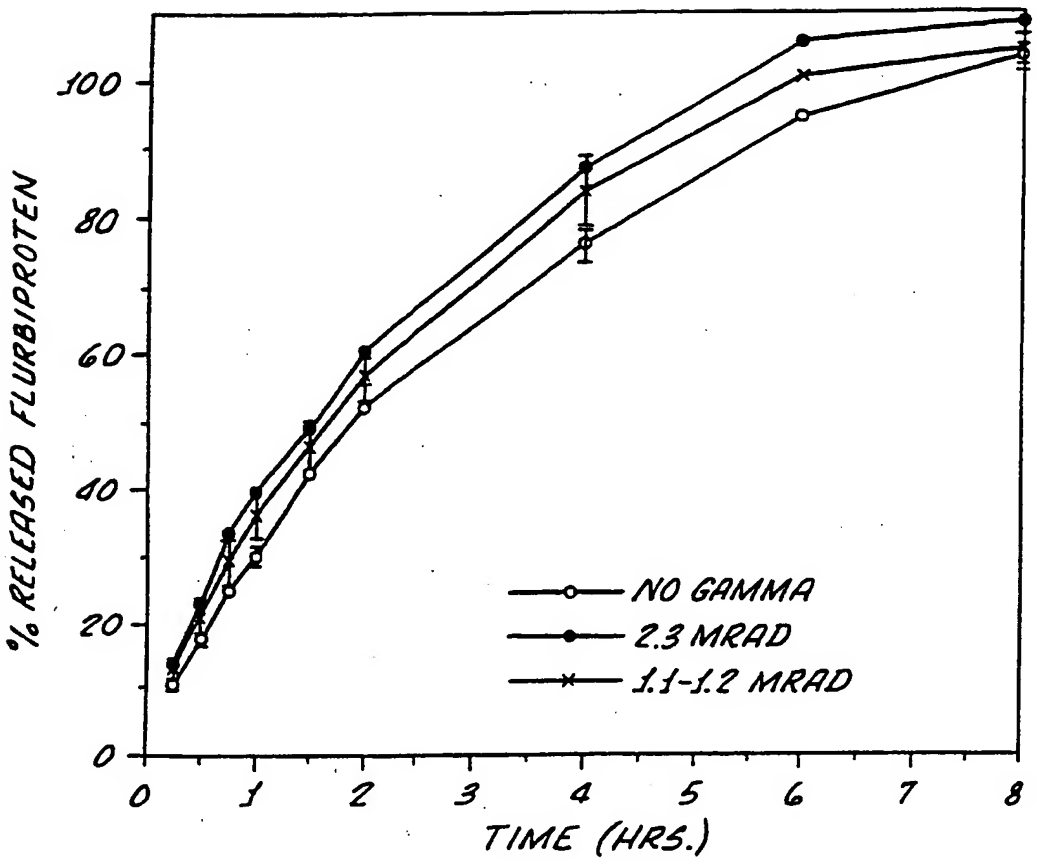
% RELEASED FLURBIPROTEN
100
80
60
40
20
0
0
1
2
3
4
5
6
7
8
TIME (HRS.)
NO GAMMA
2.3 MRAD
1.1-1.2 MRAD

FIG. 3.

IN RNATIONAL SEARCH REPORT

Inten al Application No
PCT/US 93/08020

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Week 8917, Derwent Publications Ltd., London, GB; AN 89-126026 & JP,A,1 071 822 (ROHTO PHARMACEUTICAL) 16 March 1989 see abstract	1-18
X	EP,A,0 077 261 (MERCK & CO. INC.) 20 April 1983 see the whole document	1,2, 7-12,17, 18

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 November 1993	23. 11. 93

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	VENTURA AMAT, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 93/08020

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0077261	20-04-83	CA-A- 1219213	17-03-87
		JP-A- 58075547	07-05-83
		US-A- 4730013	08-03-88